Attachment 1

Review Memo

BLA: 98-0012

Amendment: FAXed 3/26/98

Company: Centocor

Product: Infliximab

Reviewer: Kurt Brorson, Ph.D. K.B.

Through: Kathryn Stein, Ph.D.

Centocor has submitted a breakdown of infusion reactions by investigational lot of cA2. The investigational lots of cA2 had between 1.7 and 249 ppm bovine IgG. They reported infusion reaction rates from patients that had received 2 or more infusions of cA2. Crohn's patients:

Lot	*Bovine IgG (ppm)*	*reactions/ infusion*	*# infusions*	*infusions/ patient*
94D02	7.5	38.5%	26	2.2
94L02	32.1	7.8%	77	3.7
95K06	1.7	2.7%	187	3.0

All patients:

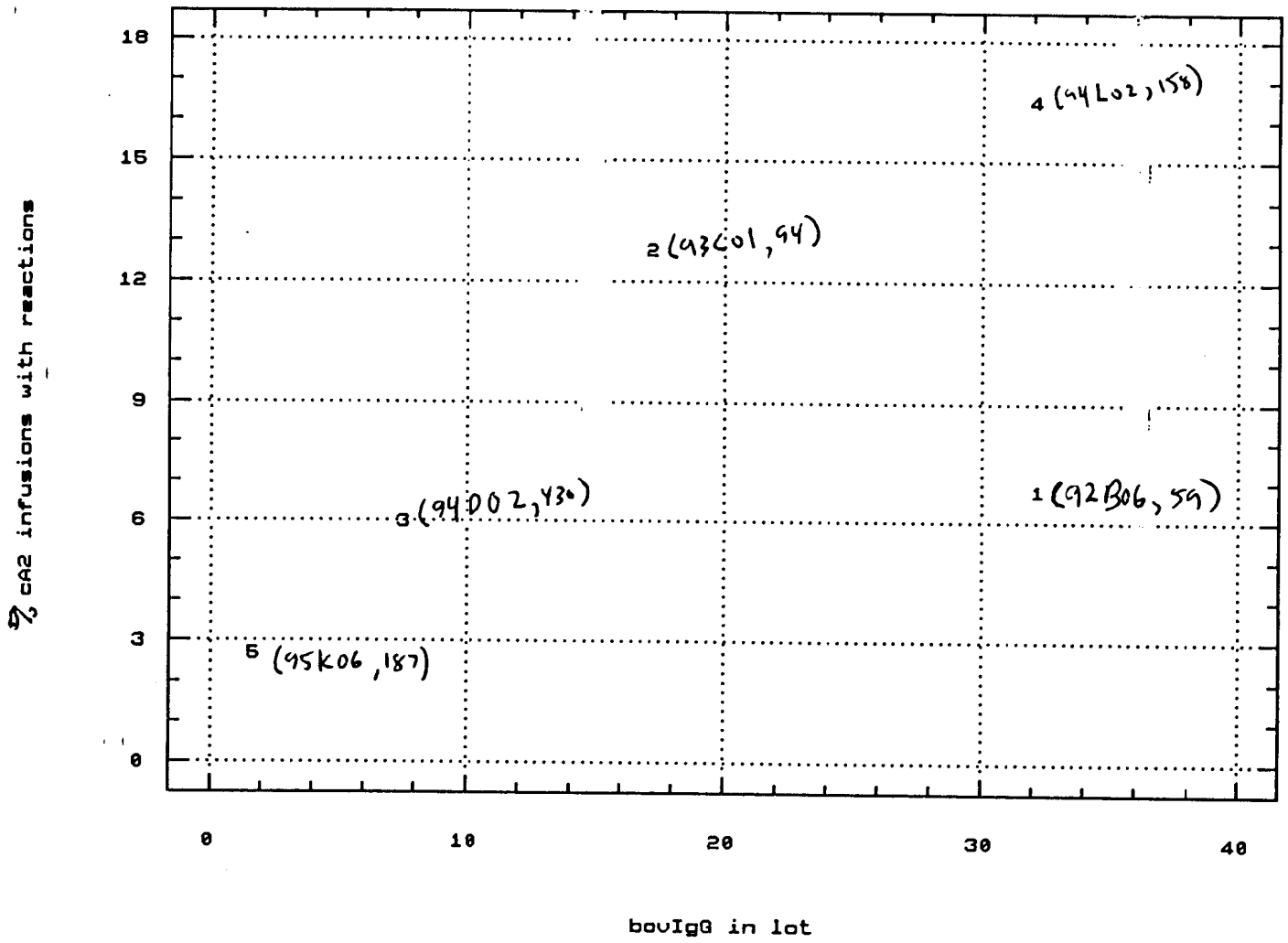
Lot	*Bovine IgG (ppm)*	*reactions/ infusion*	*# infusions*	*infusions/ patient*
92B06	32.2	6.8%	59	3.3
93C01	17.2	12.8%	94	2.0
94D02	7.5	6.0%	430	4.3
94L02	32.1	16.5%	158	3.6
95K06	1.7	2.7%	187	3.0

Combined data from all trials is probably most meaningful because the size of the data set is largest. When a scatter plot of the data is made, a rough correlation can be seen between higher rates of infusion reactions and investigational lots with higher levels of bovine IgG. For example, lot 95K06 (1.7 ppm) had the lowest rate (2.7%) and lot 94L02 (32.1 ppm) had the highest (16.5%). However, outliers are evident; lot 92B06 (32.2 ppm & 6.8%).

Reviewer's note: Centocor was asked submit a line listing by injection of lots and infusion reaction rates (

- **Centocor will set a specification for bovine IgG when 10 lots made from the — scale have been produced.**
- **Two lots made with the — scale process had 12 and 14 ppm bovine IgG, it is likely that future lots made with the — scale process will range from 10-15 ppm.**
- **The data submitted in this amendment indicate that infusion reaction rates for lots with 10-15 ppm will range between 6-13%. Even with <1 ppm (subimmunogeneic and below the level recommended by the monoclonal PTC) the infusion reaction rate was 3%. The review of the clinical data indicated that there were no severe allergic type reactions in the trial.**

Infusion reactions vs. bovIgG level
(All trials)



Attachment 2

Review Memo

BLA: 98-0012

Amendment: 4/9/98

Company: Centocor

Product: Infliximab

Reviewer: Kurt Brorson, Ph.D. 2/6

Through: Kathryn Stein, Ph.D.

Centocor has submitted information related to residual LpHse in infliximab and [redacted] cleaning validation of the lyophilizers.

FLP lots 97A07, 97A10, 97C07, 97E08, 97E09, 97K10, 97K11, 96E06, and 95K06 did not contain detectable levels of 2-phenylphenol of p-tert-amylphenol. Placebo lots 97A05, 97K13 and 95J14 also did not contain detectable levels of phenolics. The limit of detection of the HPLC assay is 0.1 ppm 2-phenylphenol and 0.4 ppm p-tert-amylphenol. Infliximab and placebo are suspended in 5 ml water to do the assay.

Based on the assay limit of detection, a patient receiving 5 mg/kg Infliximab would at most be injected with 25 ng phenylphenol/kg and 100 ng p-tert-amylphenol/kg.

The assay to detect the phenolics is a reverse-phase gradient HPLC. [redacted] HPLC column [redacted] is run using a [redacted] gradient HPLC system. The phenolics are detected as absorbence at 214 nm. The assay was validated for specificity, linearity ([redacted] accuracy and precision. No matrix effects were detected when phenolics were spiked into FLP. The LOD and LOQ for 2-phenylphenol are 0.1 ppm and 0.3 ppm. The LOD and LOQ for p-tert-amylphenol are 0.4 ppm and 1.2 ppm.

[redacted] has changed the lyophilizer cleaning procedure. They:

- [redacted]
- [redacted]
- [redacted] an
- Updated the cleaning SOP to be more specific about the procedure

On Dec 12, 1997, F validation steering committee approved a cleaning validation protocol to address removal of the two phenolics. On Jan 27, 1998, implemented the revised cleaning procedures. Scheduled lyophilization runs were performed on Jan 27 using freeze dryers . The lyophilzers were then cleaned using the new procedure. Vials from these runs were tested for phenolics and the freeze dryers were sampled by swab testing. The products that were lyophilized and tested included

Phenolics were not detected in the vials or on the swabs. The limits of detection were µg/vial and µg/swab (100 cm^2 area). **Reviewer's' note: the swabs were not tested for TOC.** They claim that based on a toxicological assessment by µg/swab is a safe level. This calculation is based on the IPR LD_{50} of 2-phenylphenol for mice.

Conclusions:

- Phenolics in the Infliximab FLP is
- If has additional cleaning validation data (e.g. TOC) and this cleaning validation is judged to be adequate, additional lots will not need to be tested.

Attachment 3

BLA Amendment Review

BLA: 98-0012

Amendment: 4/13/98

Company: Centocor

Product: Infliximab

Reviewer: Kurt Brorson, Ph.D. KB

Through: Kathryn Stein, Ph.D.

Centocor has revalidated the anion exchange columns for ERV removal. This was in response to our telecon of 2/19/98. We informed them that CBER's position was that their original studies using the — scale process were inadequate because of differences in protein loading. They repeated the validation studies using the ~~~ process.

Step	ERV removal
Primary anion exchange	>4.4 logs
Secondary anion	>4.6 logs
Total process	>20.6 logs

They have demonstrated that the manufacturing process removes — logs of ERV beyond the maximum load per dose. **Reviewers note: This data adequately addresses the retrovirus removal validation issue.**

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Attachment 6

Review Memo

BLA: 98-0012

Amendment: 5/19/98

Company: Centocor

Product: Infliximab

Reviewer: Kurt Brorson, Ph.D. KB

Through: Kathryn Stein, Ph.D.

Centocor's answers to CMC questions. Reviewer's notes are boldface:

1. SDS-PAGE analyses protein under denaturing conditions and includes a high temperature denaturing treatment that may result in some degradation. SE-HPLC measures aggregates & LMWC under native conditions, resulting in a higher purity value. **Acceptable.**

2. a. [redacted] The [redacted] bioassay measures the same thing, but is more sensitive to product degradation. They provided some data with heat stressed cA2 demonstrating that the bioassay can detect a ~50% drop in activity that the ELISA misses. **Acceptable.**

2. b. They will measure bovine IgG in each lot. They now have data from two 8kg. Scale lots Z7D117 has 14 ppm, Z7M158 has 12 ppm, results from Z7H382 are pending. They have set an alert limit of [redacted] and will establish an upper limit specification when they have data from 10 lots. **Acceptable plan if they explain what the action the alert limit triggers.**

2. c. The SOP and validation data was submitted for the bovIgG assay. The bovIgG assay is a sandwich ELISA. LOQ is 8ng/ml (0.1 ppm for 60 mg/ml cA2) and there is no cA2 matrix effect. **Acceptable.**

3. a. They don't want to set specifications for individual bands in the IEF assay. [redacted]. cA2 in contrast has a serum half life measured in days. **Acceptable.**

3. b. They changed SOP 136A to reflect our comment. **Acceptable.**

4. They don't want to incorporate an anti-C116E anti-Id control into the DRID assay because they claim that it is a non-quantitative identity test and that the ICH guidelines only require that specificity be established.

5. The don't want to repeat the RT/PCR analysis because this analysis was intended to validate that the predominant protein species has the correct sqx., not to detect variants. They cite an ICH reference on this subject.

6.) is not tested for porcine parvovirus. They have demonstrated 6.2 logs of poliovirus removal by the cA2 manufacturing scheme. Also, the

7. C. Joneckis question.

8. a. They have 6 months of stability data from 2 lots each of PFB and DPC intermediates. There were no significant product changes. They have on-going studies to

Acceptable.

8. b. C. Joneckis question.

8. c. C. Joneckis question.

9. C. Joneckis question.

10. J. Finkbohner question.

11. They went ahead and used DPC lot Z7C040 (

12. C. Joneckis question.

13. a & b. C. Joneckis question.

13. c. They don't want to validate removal of mycophenolic acid beyond the currently established [redacted], limit of detection in DPC and PFB. They cite the [redacted] licensed dose for mycophenolate mofetin. This is [redacted] higher that the highest theoretical residual MPA in infliximab. **Acceptable.**

14. C. Joneckis question.

15. Results from lot Z7H382. Purity, SDS-PAGE 98.1%, GF-HPLC >99.9. **This lot has passed specifications, acceptable.**

16. SOP 106S (SE-HPLC) was revised to stipulate that only peaks between [redacted] are used to determine product purity. They went back and recalculated the purity of several DPC lots and revised the batch records. They were all still within specifications. **Acceptable.**

17. The comparability study in volume 7 was between investigational lots. A [redacted]. They included a side-by-side analysis of potency of [redacted] scale lots in the amendment. The lots had similar potency. **Acceptable.**

18. C. Joneckis question.

19. The SOP for pH measurement is being rewritten. **This is acceptable.** It will:
    - Have separate sections for operation and programming.
    - State responsibilities for operation and programming.
    - Routine programs will be described in the quality standard manuals
    - Key functions will be described
    - Example programs will be given.

20. J. Finkbohner question.

21. J. Finkbohner question.

22. J. Finkbohner question.

23. J. Finkbohner question.

24. They will leave the moisture upper limit specification at [redacted] because they have validation data up to this range. They will evaluate stability results from future lots and revise the specification if necessary. **Acceptable.**

25. They now have 39 weeks (9 months) of stability data from lots 97E08 and 97E09. They have held these two lots at [redacted] Product held at [redacted] has accumulated visible particles outside of specifications (>F). Product held at [redacted] is still within specifications, but there is a clear trend towards the accumulation of visible particles. There is no upward trend in visible particles in product held at [redacted] Based on this data, they have revised the storage temperature to 2-8°C. **This change is warranted given their stability data, acceptable.** All other parameters are within specifications. They will submit 12 month stability data in June. [redacted]

26. Centocor has a tracking system [redacted] **This was looked at during the inspection and was found to be acceptable.**

27. They will revise the visible particle assay. They will include a new standard, [redacted]. They will incorporate 5 blinded control vials (with polystyrene beads) into the analysis. The test articles will be blinded as well. The operators will need to identify >= 80% of the blinded control vials for the assay to be valid. **These revisions are warranted given the fact that this assay is stability indicating, acceptable.**

28. The out of specification environmental monitoring results were actually transcription errors when the information was read from the [redacted] documentation. The [redacted] readings reported in the BLA were actually [redacted] **Acceptable.**

29. J. Finkbohner question

30. J. Finkbohner question

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